

RemarksI. Formal Drawings

This Application was submitted with informal drawings. Applicants submit herewith Formal Figures 1-5C on pages 1/6 to 6/6.

II. Amendment to the Drawings and Specification

Applicants have amended Figure 5 such that each of the three template structures shown in Figure 5 are now shown separately in Figures 5A through 5C. The specification has been amended to indicate this change. No new matter has been added.

III. Summary of Claim Amendments

Applicants have amended Claims 1 and 3 to indicate that the support bound starter units are provided to the biosynthetic enzymatic machinery systems *in vitro* to form a collection of template structures. Support for this amendment can be found on page 4, lines 21-22 and on page 5, lines 30-31 of the specification. In addition, Claims 1 and 3 have been amended to indicate that the biosynthetic enzymatic machinery system is selected from the group consisting of natural and modified polyketide synthases, natural and modified peptide synthetases, natural and modified terpene synthases, and natural and modified animal fatty acid synthases. Support for this amendment can be found on page 5, line 32 to page 6, line 19 of the specification.

Applicants have amended Claim 7 to remove the phrase "chemically robust functionality."

Applicants have amended Claim 10 to replace "peptide synthase" with "peptide synthetase." Support for this amendment can be found on page 5, line 33 of the specification.

Applicants have amended Claims 14 and 15 to indicate that the starter unit or the template, respectively, are purified via antibody recognition. Support for this amendment can be found on page 3, lines 24-26 and page 5, lines 12-14 of the specification).

IV. New Claims

Claim 22 is directed to a combinatorial biosynthesis method of preparing one or more compound using a peptide synthetase to catalyze a reaction between two or more amino acid derivative starter units to form a template structure. Support for this reaction can be found on page 7, lines 24-25 of the specification.

Claim 23 is directed to a combinatorial biosynthesis method of preparing one or more compound using a polyketide synthase to catalyze a reaction between two or more thioester derivative starter units to form a template structure. Support for this reaction can be found on page 7, lines 12-13 of the specification. In addition, Figs. 1 and 2(3) show the structures of several representative thioester derivatives.

Support for modifying starter units (e.g., amino acid derivative or thioester derivatives) to include a functional handle selected from the group consisting of alkynes, olefins and iodoalkenes can be found on page 8, lines 5-19 of the specification.

Support for reacting functional handles with solid supports containing an alkyne or an olefin group via a Glaser coupling, olefin metathesis or a Stille coupling reaction can be found on page 9, lines 16-26 of the specification.

Support for functionalizing a template structure with the reactions listed in step c) can be found on page 14, lines 8-27 of the specification.

V. Summary of the Claimed Invention

Applicants claim a method of preparing one or more compounds that involves providing one or more starter unit that is capable of being accepted by one or more modular biosynthetic enzymatic machinery system. Examples of modular biosynthetic enzymatic machinery systems include fatty acid synthase, polyketide synthase, peptide synthetase or terpene synthase (page 5, line 32 to page 6, line 5 of the specification). The type of starter unit selected is dependent on the modular biosynthetic enzymatic machinery system used (page 7, lines 20-22 of the specification). For example, if peptide synthetase is selected as the modular biosynthetic enzymatic machinery system, starter units are amino acid derivatives (page 7, lines 24-25 of the specification). Whereas, when a polyketide synthase is used as the modular biosynthetic enzymatic machinery system, thioesters derivatives are used as starting materials (page 7, lines 12-14 of the specification and Figs. 1 and 2, Example 3). One or more of the starter units

includes a functional handle that is reacted with a functionality present on a solid support to form one or more support bound starter unit. For example, the starter unit can include, or be modified to include, an alkyne (page 8, lines 20-25 of the specification and Fig. 3), which can be coupled to a solid support that has an alkyne functional group via a Glaser Coupling reaction (page 9, lines 16-22 of the specification). The support bound starter units are provided to one or more modular biosynthetic enzymatic machinery system to generate a collection of template structures which are functionalized with synthetic organic chemistry. This collection may be provided to the modular biosynthetic enzymatic machinery system and functionalized with synthetic organic chemistry one or more time until the desired support bound collection of structures is generated.

VI. Rejections of Claims 1-3 and 5-21 Under 35 U.S.C. § 112, First Paragraph

A. Written Description

1. Summary of the Examiner's Rejection

The Examiner states that Claims 1-3 and 5-21 contain subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner states that the claims encompass a broad genus but the specification does not disclose representative examples of a "support bound starter unit," a "template structure," a "species of template structure after functionalization," a "nonnatural natural product," or an "antibody recognition element." In addition, the Examiner states that the specification and the claims do not provide any guidance as to what structural feature all of these reagents and products share. Therefore, the Examiner takes the position that there is no teaching that would allow a person of skill in the art to determine all the different types of compounds that should be included in the genus.

2. Claims 1-3 and 5-21

Since Applicants are not claiming a genus of compounds, but instead are claiming a method of making a combinatorial library that exhibits a high degree of structural diversity, it is irrelevant and, in fact, may be undesirable, for the products of the method to have a common structural feature. Although it is possible to create a library in which the members have a common structural feature using the method of the invention, Applicants' specification makes it

clear that, at least in some embodiments, it would be more desirable if the products of the method of the invention do not have a common structural feature because this would make the library more structurally diverse (see page 2, lines 28-31 of the specification).

The Examiner has also takes the position that the specification does not provide adequate written description of the method of the invention because the specification does not provide any guidance as to what structural features all of the reagents used in the method of the invention share. Applicant respectfully disagree with the Examiner. Applicants state on page 7, lines 20-22 of the specification that since the biosynthetic enzymatic machinery system catalyzes the generation of template structures from starter units, the required common structural feature(s) of the starter units are defined by the biosynthetic enzymatic machinery system employed. Applicants have provided several examples of biosynthetic enzymatic machinery systems and have indicated what common structural features the starter units should have. Examples of biosynthetic enzymatic machinery systems disclosed in the specification include animal fatty acid synthase, polyketide synthase, peptide synthetase, and terpene (or isoprenoid) synthase (see page 5, line 32 to page 6, line 5 of the specification).

In addition, Applicants have described modified enzymatic pathways by incorporating by reference U.S. Patent Application Serial No. 09/225,990 (now U.S. Patent No. 6,358,712), which discloses a method preparing modified enzymatic machinery, such as polyketide synthases, peptide synthetase, terpene synthases, and fatty acid synthases (see Exhibit A, U.S. Patent No. 6,358,712, Col. 16, lines 38-65). For example, polyketide synthase, peptide synthetases, terpene synthases, and animal fatty acid synthases each have functional domains, the order or number of which can be shuffled to create modified enzymes. U.S. Patent No. 6,358,712 also provides a method of producing polyketide synthases with PKS functional domains from different microbial strains (Exhibit A, Col. 18, lines 18-48). Applicants have stated that these mutated biosynthetic enzymatic systems can be used to create "unnatural" natural products (see page 10, lines 8-10 of the specification).

Applicants have disclosed that polyketide synthases will accept starter units that have a thioester group and that these starter units can be used to generate template structures such as those shown in Figure 1 of the instant application (see page 7, lines 8-14 of the specification).

Applicants have disclosed that a terpene synthase will utilize starter units that are derivatives of farnesyl pyrophosphate (see page 7, lines 22-24 of the specification) and have shown in Figure 2, example 1 the structure of a typical starter unit that can be accepted by terpene synthase.

Applicants have disclosed that when the enzymatic machinery is a peptide synthetase, the starter unit should be an amino acid derivative (page 7, lines 24-25 of the specification). In addition, Applicants have shown in Figure 2, example 2 a typical example of a starter unit that can be accepted by peptide synthetase. It is known in the art that peptide synthetases catalyze reactions between starter units that have a carboxylic acid and a primary or secondary amine group (such as found in natural amino acids). Thus, derivatives of amino acids that have both a carboxylic acid and a primary or secondary amine group would be suitable starter units for peptide synthetases.

Furthermore, Applicants have indicated that functional starter units that will be accepted by the selected enzymatic machinery can be identified by presenting a random set of starter units having a common structural feature to an enzymatic machinery system (e.g., a thioester group for a polyketide synthase or an amino acid derivative having a carboxylic acid group and a primary or secondary amine group for a peptide synthetase) (see page 7, lines 14-19 of the specification).

The template molecules produced by each of the enzymatic machinery systems can vary widely in structure depending on the starter units available to the enzymatic machinery. Thus, the method of the invention can produce a combinatorial library that is not limited to compounds that have a common core structure. Applicants have provided several examples of templates that can be produced using polyketide synthase and several different starter units in Fig. 1.

Applicants have disclosed that the template molecules produced by the enzymatic machinery are selected or designed to have latent functionalities that can be functionalized using synthetic organic chemistry on page 13, lines 29-31 of the specification. Applicants provide several examples of the types of reactions that can be used to functionalize template molecules. For example, Applicants disclose that hydroxyl groups can be functionalized with electrophiles such as isocyanates, anhydrides or acid chlorides; epoxide groups may be reacted with nucleophiles, such as amines; iodo groups on aromatic rings may be converted to amines, amides, aromatic rings, alkenes, alkynes or heterocycles using palladium catalyzed reactions.

such as Buchwald-Hartwig aminations, Heck and Stille couplings, Sonogashira/Castro-Stephens couplings, Suzuki and Stille couplings and carbonylations; aryl alkynes can undergo rhodium-catalyzed hydroacylation, azide cycloaddition, nitrone cycloaddition, and nitrile oxide cycloaddition; and amides can be functionalized using a Mitsunobu reaction to generate an alcohol (page 14, lines 14-27 of the specification).

The Examiner has stated that Applicants do not have any representative example of an "antibody recognition element." Applicants have disclosed that an antibody recognition element is a group that is capable of being recognized by an antibody (see page 5, line 12-14 of the specification). Applicants use the antibody recognition element to purify the products of the enzymatic machinery. Therefore, Applicants' invention is not limited to any particular antibody recognition element. Many groups that are recognized by particular antibodies are known in the art. In addition, it is well known in the art that monoclonal antibodies can be prepared that recognize almost any functional group desired by injecting an antigen which contains the group into an animal, such as a mouse. Such techniques are described in any standard biology textbook, such as in Stryer, *Biochemistry*, 3rd Edition, W.H. Freeman and Company, New York, 1988, pages 895-897 (see Exhibit B).

The Examiner has stated that Applicants do not have any species of solid support listed in the specification. Solid supports are well known in the art and can be purchased through many vendors. Applicants have listed in the specification the properties which a solid support should have to be useful in the method of the invention. For example, Applicants state that solid supports should have a functional group that can bind to a handle on a starter unit, such as an alkyne, olefin or iodoalkene (page 8, lines 16-26 of the specification). Applicants list Glaser coupling, olefin metathesis and Stille Coupling reactions for coupling alkynes, olefins and iodoalkenes to solid supports that have one or more alkyne or olefin groups (see page 9, lines 16-29 of the specification).

Applicants have described how to select starter units that are compatible with a particular enzymatic machinery, and how to select solid supports that can be attached to the handles present on the starter units and incorporated into the template structures formed by the enzymatic machinery. Applicants have not described common structural features of the products of the inventive method because Applicants' method is designed to create products with a large amount

of diversity. Thus, Applicants' specification clearly conveys that Applicants had possession of the claimed method at the time the application was filed.

2. New Claims

The specification provides written description for new Claims 22 and 23. Claim 22 is directed to a combinatorial biosynthesis method of preparing one or more compound using a peptide synthetase to catalyze reaction between two or more amino acid derivative starter units to form a template structure. Applicants describe using a peptide synthetase to catalyze the coupling of amino acid derivatives on page 7, lines 24-25 of the specification. Since the starter units are amino acid derivatives, they all have the common structural features of a carboxylic acid and a primary or secondary amine group.

Claim 23 is directed to a combinatorial biosynthesis method of preparing one or more compound using a polyketide synthase to catalyze a reaction between two or more thioester derivative starter units to form a template structure. Applicants describe using a polyketide synthase to catalyze the coupling of starter units that have the common structural feature of a thioester group on page 7, lines 12-13 of the specification.

Applicants disclose that starter units (e.g., amino acid derivative or thioester derivatives) can be modified to include a functional handle selected from the group consisting of alkynes, olefins and iodoalkenes on page 8, lines 5-19 of the specification, and disclose that the functional handles can be reacted with solid supports containing an alkyne or an olefin group via a Glaser coupling, olefin metathesis or a Stille coupling reaction on page 9, lines 16-26 of the specification.

On page 14, lines 8-27 of the specification, Applicants disclose that template structures can be functionalized using nucleophilic addition, functionalization of hydroxyl groups with electrophiles, Buchwald-Hartwig aminations, Heck coupling, Stille coupling, Sonogashira/Castro-Stephens coupling, Suzuki coupling, carbonylations, Mitsunobu reaction, hydroacylation, azide cycloaddition, nitrone cycloaddition, and nitrile oxide cycloaddition.

Since Applicants have disclosed common structural features for starter units that are accepted by polyketide synthase and peptide synthetase and have described in the specification

the specific reactions used to modify template structures, the specification conveys that Applicants had possession of the method of Claims 22 and 23 at the time the invention was filed.

B. Enablement

1. Summary of the Examiner's Rejection

The Examiner has rejected Claims 1-3 and 5-21 under 35 U.S.C. §112, first paragraph. The Examiner states that Applicants have provided no examples of a solid support unit which the Examiner states is a critical element to all of Applicants' claimed embodiments. The Examiner takes the position that a person of skill in the art would not know how to place a support bound starter unit inside a host cell in such a way as to insure its interaction with the host biosynthetic enzymatic machinery without at least one example from Applicants. The Examiner also states that it has not been shown that the enzymes in a modular enzymatic machinery could accommodate a solid support or that a support bound starter unit could be transferred from one enzyme to the next in the modular enzymatic machinery. In addition, the Examiner states that combinatorial biology is an unpredictable field and that Applicants have provided no specific guidance as to reagents and products that are essential for the method of the invention. The Examiner concludes that a person of skill in the art would not know how to practice the claimed invention without undue experimentation because the specification provides no working examples and the genus claimed is broad.

2. Claims 1-3 and 5-21

Applicants disagree with the Examiner's conclusion that a person skilled in the art would not be able to practice Applicants' claimed invention without undue experimentation. Applicants' specification discloses on page 7, lines 20-22 that since the biosynthetic enzymatic machinery system catalyzes the generation of template structures from starter units, the type of starter unit is dependent on the biosynthetic enzymatic machinery system used. Applicants have provided several examples of biosynthetic enzymatic machinery system and have indicated what common structural features the starter units should have. Examples of biosynthetic enzymatic machinery system disclosed in the specification include animal fatty acid synthase, polyketide

synthase, peptide synthetase, and terpene (or isoprenoid) synthase (see page 5, line 32 to page 6, line 5 of the specification).

In addition, Applicants have incorporated by reference U.S. Patent Application Serial No. 09/225,990 (now U.S. Patent No. 6,358,712), which discloses a method preparing modified enzymatic machinery, such as polyketide synthases, peptide synthetase, terpene synthases, and animal fatty acid synthases (see Exhibit A, U.S. Patent No. 6,358,712, Col. 16, lines 38-65). For example, polyketide synthase, peptide synthetases, terpene synthases, and animal fatty acid synthases each have functional domains, the order or number of which can be shuffled to create modified enzymes. U.S. Patent No. 6,358,712 also provides a method of producing polyketide synthases with PKS functional domains from different microbial strains (Exhibit A, Col. 18, lines 18-48). Applicants have disclosed that these mutated biosynthetic enzymatic machinery systems can be used to create "unnatural" natural products (see page 10, lines 8-10 of the specification).

Applicants have disclosed that polyketide synthases will accept starter units that have a thioester group and that these starter units can be used to generate template structures such as those shown in Figure 1 of the instant application (see page 7, lines 8-14 of the specification).

Applicants have disclosed that a terpene synthase will utilize starter units that are derivatives of farnesyl pyrophosphate (see page 7, lines 22-24 of the specification) and have shown in Figure 2, example 1 the structure of a typical starter unit that can be accepted by terpene synthase.

Applicants have disclosed that when the enzymatic machinery is a peptide synthetase, the starter unit should be an amino acid derivative (page 7, lines 24-25 of the specification). In addition, Applicants have shown in Figure 2, example 2 a typical example of a starter unit that can be accepted by peptide synthetase. It is known in the art that peptide synthetases catalyze reactions between starter units that have a carboxylic acid and a primary or secondary amine group (such as found in natural amino acids). Thus, derivatives of amino acids that have both a carboxylic acid and a primary or secondary amine group would be suitable starter units for peptide synthetases.

Furthermore, Applicants have indicated that functional starter units that will be accepted by the enzymatic machinery can be identified by presenting a random set of starter units having a

common structural feature to an enzymatic machinery system (e.g., a thioester group for a polyketide synthase or an amino acid derivative having a carboxylic acid group and a primary or secondary amine group for a peptide synthetase) (see page 7, lines 14-19 of the specification). A person skilled in the art would not need to do undue experimentation to select an enzymatic system and the starter units that would be accepted by the enzymatic system because Applicants have disclosed how to select starter units for natural and modified polyketide synthases, peptide synthetases, terpene synthases, and animal fatty acid synthases.

Applicants have disclosed synthetic organic chemistry reactions that can be used to functionalize particular latent functionalities of template molecules. For example, Applicants disclose that hydroxyl groups can be functionalized with electrophiles such as isocyanates, anhydrides or acid chlorides; epoxide groups may be reacted with nucleophiles, such as amines; iodo groups on aromatic rings may be converted to amines, amides, aromatic rings, alkenes, alkynes or heterocycles using palladium catalyzed reactions, such as Buchwald-Hartwig aminations, Heck and Stille couplings, Sonogashira/Castro-Stephens couplings, Suzuki and Stille couplings and carbonylations; aryl alkynes can undergo rhodium-catalyzed hydroacylation, azide cycloaddition, nitrone cycloaddition, and nitrile oxide cycloaddition; and amides can be functionalized using a Mitsunobu reaction to generate an alcohol (page 14, lines 14-27 of the specification). Thus, a person skilled in the art would know how to functionalize template molecules given the guidance of Applicants' specification.

The Examiner has stated that Applicants do not have any representative example of an "antibody recognition element." Applicants have disclosed that an antibody recognition element is a group that is capable of being recognized by an antibody (see page 5, line 12-14 of the specification). Applicants use the antibody recognition element to purify the products of the enzymatic machinery. Therefore, Applicants' invention is not limited to any particular antibody recognition element. Many groups that are recognized by particular antibodies are known in the art. In addition, it is well known in the art that monoclonal antibodies can be prepared that recognize almost any functional group desired by injecting an antigen which contains the group into an animal, such as a mouse. Such techniques are described in any standard biology textbook, such as in Stryer, *Biochemistry*, 3rd Edition, W.H. Freeman and Company, New York, 1988, pages 895-897 (see Exhibit B).

The Examiner has stated that a person skilled in the art would not know how to place a support bound starter unit in a host cell. Applicants disagree with the Examiner's assertion. However, in order to expedite prosecution, Applicants have amended the claims to indicate that the starter units are provided to the enzymatic machinery *in vitro*, thus rendering this part of the rejection moot.

The Examiner has also stated that a person skilled in the art would not know how to select a solid support that would insure the reaction between the enzymatic machinery and the support bound starter unit. Applicants have disclosed in the specification that support bound starter units will be accepted by the biosynthetic enzymatic machinery and research has indicated that biosynthetic enzymatic machinery systems will tolerate broad variation in starter units (see Exhibit C: Weissman, *et al.*, *Chemistry & Biology* (1998), 5(12):743-754 at page 743, the paragraph labeled "Conclusions"). The court has stated that the following regarding the Examiner's burden of proof when making an enablement rejection

... it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertion of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971)

In the instant case, evidence indicates that biosynthetic enzymatic machinery systems can tolerate a broad variation in starter units which supports Applicants' disclosure that support bound starter units will be tolerated by biosynthetic enzymatic machinery systems. The Examiner has not provided any evidence to the contrary. Thus, the Examiner has not met his burden of establishing a reasonable basis for questioning whether biosynthetic enzymatic machinery systems can accept support bound starter units.

In addition, Applicants have disclosed in the specification the properties which a solid support should have to be useful in the method of the invention. For example, Applicants state

that solid supports should have a functional group that can bind to a handle on a starter unit, such as an alkyne, olefin or iodoalkene (page 8, lines 16-26 of the specification). Applicants list Glaser coupling, olefin metathesis and Stille Coupling reactions for coupling alkynes, olefins and iodoalkenes to solid supports that have one or more alkyne or olefin groups (see page 9, lines 16-29 of the specification).

Applicants have described how to select starter units that are compatible with a particular enzymatic machinery, and how to select solid supports that can be attached to the handles present on the starter units and incorporated into the template structures formed by the enzymatic machinery. Thus, the teachings of Applicants' specification would allow a person skilled in the art to practice Applicants' claimed method without undue experimentation.

3. New Claims 22 and 23

Applicants' specification teaches the type of starter units to be used with peptide synthetase (page 7, lines 24-25 of the specification) and polyketide synthase (page 7, lines 12-13 of the specification) and teaches which reactions to use to functionalize the template structures formed by the enzymatic systems (page 14, lines 8-27 of the specification). Applicants teach how to prepare a starter unit that is attached to a solid support (on page 9, lines 16-26 of the specification), and, as discussed above, the enzymatic systems can tolerate a broad range of structural variation in starter units and, therefore, could accept a support bound starter unit as a substrate. Thus, a person skilled in the art, given the guidance of Applicants' specification, would be able to practice Applicants' method of Claims 22 and 23 without undue experimentation.

VII. Rejections Under 35 U.S.C. § 112, Second Paragraph

A. "Starter Units"

The Examiner has rejected Claims 1, 3, 8, and 14 because the Examiner takes the position that the term "starter unit" is defined only by functional properties and not by any chemical or physical characteristic. The Examiner states that "A claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention." The Examiner cites *Ex parte Pulvarti* 157 U.S.P.Q. 169 to support this point.

The prohibition against claiming a material that is defined solely in functional terms does not apply to the instant claims because Applicants are not claiming a material. In the instant case, Applicants are claiming a method in which some of the elements are defined functionally. The opinion in *Ex parte Pulvari* distinguishes between the case where a material is defined solely in functional terms, which is unpatentable, and the case where there is a combination of substances wherein only an element is defined in functional terms, which can be patentable. *Ex parte Pulvari*, 157 U.S.P.Q. 169, 171 (P.O.B.A. 1967).

M.P.E.P. § 2173.05(g) states the following regarding functional limitations:

There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 U.S.P.Q. 226 (CCPA 1971).

A functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used.

Applicants have defined "starter units" as any compound that is capable of being utilized by an enzymatic pathway (see page 7, lines 29-32 of the specification). Thus, under Applicants' definition, the enzymatic pathway used will determine the chemical and structural limitations of the starter units. Applicants indicate chemical and structural limitations for starter units that are accepted by several biosynthetic enzymatic machinery systems of several enzymatic pathways. For example, Applicants disclose that when polyketide synthases are used as the enzymatic machinery, starter units have a thioester group (see page 7, lines 12-14 of the specification). Applicants have indicated that a terpene synthase will utilize starter units that are derivatives of farnesyl pyrophosphate (see page 7, lines 22-24 of the specification) and have shown in Figure 2, example 1 the structure of a typical starter unit that can be accepted by terpene synthase. Applicants have disclosed that when the enzymatic machinery is a peptide synthetase, the starter unit should be an amino acid derivative (page 7, lines 24-25 of the specification). In addition, Applicants have shown in Figure 2, example 2 a typical example of a starter unit that can be accepted by peptide synthetase. Thus, Applicants' specification makes it clear to a person of skill in the art that the term "starter units" is any compound accepted by a particular enzymatic

system and what structural features a starter unit needs to have to be utilized by a particular enzymatic system.

B. "Handles"

The Examiner has rejected Claims 1, 3, and 7 because the Examiner takes the position that the term "handle" is defined only by functional properties and not by any chemical or physical characteristic.

As discussed in the section above, it is permissible to define elements of a claim in functional terms, and functional limitations should be evaluated and considered, like any other limitation of the claim, for what it fairly conveys to a person of skill in the pertinent art in the context in which it is used.

Applicants have defined "handles" as a functional group that is capable of attachment to a functionality present on a solid support (see page 8, lines 5-8 of the specification). Applicants have disclosed that handles are preferably functional groups that are capable of withstanding the reaction conditions encountered in the enzymatic machinery (see page 8, lines 14-17 of the specification) and have listed alkynes, olefins and iodoalkenes are examples of handles that can be used in the method of the invention (see page 8, lines 17-19 of the specification). Thus, using Applicants specification a person skilled in the art could determine which groups could be used as handles.

C. "Collection of Structures"

The Examiner has stated that there is insufficient basis for the limitation "collection of structures" in Claim 3 and suggests that Applicants substitute the phrase "collection of template structures."

Applicants have adopted the Examiner's suggestion.

D. "Chemically Robust Functionality"

The Examiner states that the phrase "chemically robust functionality" in Claim 7 is indefinite because the Examiner takes the position that the specification does not provide a

standard for ascertaining the requisite degree. Thus, the Examiner states that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicants have removed the phrase "chemically robust functionality" from Claim 7, thus obviating the rejection.

E. "Modified Enzymes"

The Examiner states that the term "modified" in Claim 11 is indefinite because the Examiner takes the position that the specification does not provide a standard for ascertaining the requisite degree. Thus, the Examiner states that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicants have indicated that the term "modified enzymes" is any biosynthetic enzyme in which the catalytic properties has been altered by human intervention (see page 6, lines 8-13 of the specification). A person skilled in the art could determine whether the catalytic activity of a biosynthetic enzyme has been modified by human intervention. Thus, the scope of Claim 11 and the claims depending therefrom is clear.

F. "Antibody Recognition Element"

The Examiner has rejected Claims 14 and 15 because the Examiner takes the position that the term "antibody recognition element" is defined only by functional properties and not by any chemical or physical characteristic.

Applicants have removed the phrase "antibody recognition element" from Claims 14 and 15, thus obviating the rejection.

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Page 23 of 23

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